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=> d his 1

     (FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, WPIDS, SCISEARCH, AGRICOLA'
     ENTERED AT 14:55:20 ON 20 SEP 2004)
L33           48 DUP REM L2 L32 (26 DUPLICATES REMOVED)

=> d que l33
L1             3 SEA FILE=REGISTRY ^LVRIPLHKFT/SQSP
L2             4 SEA FILE=HCAPLUS L1
L3            79 SEA MORIKAWA W?/AU
L9         21081 SEA (L3 OR L4 OR L5 OR L6 OR L7 OR L8)
L10           60 SEA L9 AND INHIBIT?(5A)(METASTA? OR CANCER?)
L11            1 SEA L10 AND ASPART?
L12            0 SEA (ASPARTIC OR ASPARTASE#)(3A) ENZYM?(5A) INHIBIT?(5A)(METAST
                 A? OR CANCER?)
L13            0 SEA (ASPARTIC OR ASPARTASE#)(5A) ENZYM?(5A) INHIBIT?(5A)(METAST
                 A? OR CANCER?)
L14         1210 SEA PLASMA(5A) PROTEIN# (5A)(FRAGMENT? OR PEPTIDE#)
L15            2 SEA L14 AND INHIBIT?(5A)(METASTA? OR CANCER? OR CARCINO? OR
                 NEOPLAS?)
L16          366 SEA CATHEPSIN(2A) D(5A) PRECURSOR?
L17            2 SEA L16 (5A) HOMOLOG?
L18       306711 SEA (PLASMINOGEN# OR FIBRONECTIN# OR VITRONECTIN# OR HEPATOCYTE
                 (3A) GROWTH(3A) FACTOR#)
L19          293 SEA L18 (5A)(FRAGMENT? OR PEPTIDE#) AND INHIBIT?(5A)(METASTA?
                 OR CANCER? RO CARCINO? OR NEOPLAS?)
L20           33 SEA L19 AND ENZYM?
L21           31 SEA L19 AND (PROTEASE? OR PROTEINASE?)
L22           50 SEA L19 AND KRINGLE?
L23            6 SEA L22 AND(KDA OR KD OR KILODALTON?)
L24           22 SEA L16 AND RELATE?
L25            6 SEA L24 AND (METASTA? OR CANCER? OR CARCINO? OR NEOPLAS?)
L26           16 SEA L24 NOT L25
L27            4 SEA L26 AND ASPART?
L28         7527 SEA ASPART? (3A) PROTEASE?
L29           38 SEA L28 AND INHIBIT? (5A)(METASTA? OR CANCER? OR CARCINO? OR
                 NEOPLAS?)
L30          103 SEA (L11 OR L12 OR L13) OR L15 OR L17 OR L20 OR L21 OR L23 OR
                 L25 OR L27 OR L29
L31           70 SEA L30 NOT PY>2001
L32           70 SEA L31 OR L11
L33           48 DUP REM L2 L32 (26 DUPLICATES REMOVED)


=> d ibib abs l33 1-48

L33  ANSWER 1 OF 48  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:    2001397797  EMBASE
TITLE:               p22 is a novel plasminogen fragment
                     with antiangiogenic activity.
AUTHOR:              Kwon M.; Yoon C.-S.; Fitzpatrick S.; Kassam G.; Graham
                     K.S.; Young M.K.; Waisman D.M.
CORPORATE SOURCE:    D.M. Waisman, Cancer Biology Research Group, Department of
                     Biochemistry, University of Calgary, Calgary, Alta. T2N
                     4N1, Canada. waisman@ucalgary.ca
SOURCE:              Biochemistry, (6 Nov 2001) 40/44 (13246-13253).
                     Refs: 38
                     ISSN: 0006-2960  CODEN: BICHAW
```

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Tumor or tumor-associated cells cleave circulating plasminogen into three or four **kringle**-containing antiangiogenic fragments, collectively referred to as angiostatin. Angiostatin blocks tumor growth and metastasis by preventing the growth of endothelial cells that are critical for tumor vascularization. Here, we show that cancer and normal cells convert **plasminogen** into a novel 22 **kDa** **fragment** (p22). Production of this **plasminogen** **fragment** in a cell-free system has allowed characterization of the structure and activity of the protein, p22 consists of amino acid residues 78-180 of plasminogen and therefore embodies the first plasminogen **kringle** (residues 84-162) as well as additional N- and C-terminal residues. Circular dichroism and intrinsic fluorescence spectrum analysis have defined structural differences between p22 and recombinant plasminogen **kringle** 1 (rK1), therefore suggesting a unique conformation for **kringle** 1 within p22. Proliferation of capillary endothelial cells but not cells of other lineages was selectively inhibited by p22 in vitro. In addition, p22 prevented vascular growth of chick chorioallantoic membranes (CAMs) in vivo. Furthermore, administration of p22 at low dose suppressed the growth of murine Lewis lung carcinoma (LLC) metastatic foci in vivo. This is the first identification of a single **kringle**-containing antiangiogenic **plasminogen** **fragment** produced under physiological conditions.

L33 ANSWER 2 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2001:887933 HCAPLUS
DOCUMENT NUMBER: 137:72704
TITLE: Inhibition of tumor growth by plasminogen-related protein-B
AUTHOR(S): Lewis, Valerae O.; O'Reilly, Michael S.; Gehrmann, Marion; Llinas, Miguel; Schaller, Johann; Weissbach, Lawrence
CORPORATE SOURCE: Orthopaedic Research Laboratories, Massachusetts General Hospital and Harvard Medical School, Boston, MA, 02114, USA
SOURCE: Anticancer Research (2001), 21(4A), 2287-2291
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Various **fragments** of the fibrinolytic protein **plasminogen** can act as antiangiogenic factors and **inhibit** the growth of primary and **metastatic** tumors in mice. Plasminogen-related gene-B encodes a putative 9 kDa protein virtually identical to the **plasminogen** N-terminal activation **peptide**, a 77-amino acid motif that is liberated from the parent plasminogen mol. during conversion to the serine **proteinase** plasmin. Previous data have documented enhanced transcription of plasminogen-related gene-B in neoplastic tissues. We have tested the effects of recombinant versions of plasminogen-related protein-B and the **plasminogen** N-terminal activation **peptide** on the growth of tumors in mice, employing murine tumor cell lines implanted s.c. The recombinant plasminogen-related protein-B significantly inhibited the

growth of primary tumors in mice, while recombinant **plasminogen** N-terminal activation **peptide** elicited only a slight inhibition of tumor growth. These data suggest that plasminogen-related protein-B may have utility as a novel cancer therapeutic.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2000:241459 HCAPLUS
DOCUMENT NUMBER: 132:275964
TITLE: Novel human aspartase homologous to cathepsin D precursor and use for producing anti-metastasis plasma protein fragments
INVENTOR(S): Morikawa, Wataru; Kaminaka, Kazuyoshi; Takemoto, Sumiyo; Maeda, Hiroaki; Nozaki, Chikateru; Miyamoto, Seiji
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020570	A1	20000413	WO 1999-JP5322	19990929
W: US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 2000106882	A2	20000418	JP 1998-296095	19981002
EP 1118660	A1	20010725	EP 1999-970118	19990929
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: JP 1998-296095 A 19981002
WO 1999-JP5322 W 19990929

AB A novel aspartase, PACE4 (plasminogen angiostatin converting enzyme of pH 4), is prepared from cell line PC-3 that was established from human prostate cancer and characterized. PACE4 exhibits a mol. weight of 45 kDa as determined by non-reducing SDS-PAGE and LVRIPLHKFT at the N-terminus. PACE4 aspartase is highly homol. to human cathepsin D precursor and can degrade plasma proteins such as plasminogen, fibronectin, vitronectin, and human hepatic growth factor into fragments that have the angiostatin-like activities and thus the anti-metastasis effects. A pharmaceutical composition containing PACE4 for the prevention of treatment of solid cancers, diabetic retinopathy, or rheumatism is also claimed.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 4 OF 48 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-475705 [41] WPIDS
DOC. NO. NON-CPI: N2000-354888
DOC. NO. CPI: C2000-142585
TITLE: High-throughput methods for identifying modulators of protease activity comprises exposing an alpha-donor fusion polypeptide to a protease to allow protease

cleavage, and measuring the resulting beta-galactosidase activity.

DERWENT CLASS: B04 D16 S03
INVENTOR(S): MENZEL, R; WANG, S
PATENT ASSIGNEE(S): (SMAL-N) SMALL MOLECULE THERAPEUTICS INC
COUNTRY COUNT: 89
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000039348	A1	20000706	(200041)*	EN	34
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW					
AU 2000022178	A	20000731	(200050)		
EP 1141419	A1	20011010	(200167)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000039348	A1	WO 1999-US31026	19991223
AU 2000022178	A	AU 2000-22178	19991223
EP 1141419	A1	EP 1999-966678	19991223
		WO 1999-US31026	19991223

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000022178	A	Based on	WO 2000039348
EP 1141419	A1	Based on	WO 2000039348

PRIORITY APPLN. INFO: US 1998-113589P 19981224
AN 2000-475705 [41] WPIDS
AB WO 200039348 A UPAB: 20000831
NOVELTY - Identifying modulators (I) of protease activity comprising assays that detect and measure the level of beta -galactosidase activity.

DETAILED DESCRIPTION - (I) comprises:

(a) contacting a test compound with a cell or a sample comprising an alpha -donor fusion polypeptide, a protease, and an alpha -acceptor, under conditions and for a period sufficient for protease cleavage, where the alpha -donor fusion polypeptide comprises an alpha -donor in operative association with a protease substrate, and where protease cleavage of the alpha -donor fusion polypeptide results in beta -galactosidase activity;

(b) measuring the level of beta -galactosidase activity; and

(c) comparing the level of beta -galactosidase activity in (b) to the level obtained in the absence of the test compound. If the level in (b) differs from that obtained in the absence of the test compound, a compound that modulates the activity of a protease is identified.

INDEPENDENT CLAIMS are also included for the following:

(1) a cell comprising a nucleic acid molecule or molecules that express an alpha -donor fusion polypeptide, a protease, and an alpha -acceptor, where the alpha -donor fusion polypeptide has an alpha -donor

in operative association with a protease substrate, and where protease cleavage of the alpha -donor fusion polypeptide results in beta -galactosidase activity;

(2) an alpha -donor fusion polypeptide comprising an alpha -donor in operative association with a protease substrate;

(3) a kit for identifying modulators of protease activity;

(4) a compound that inhibits protease activity identified by the methods; and

(5) treating a patient with an infectious disease comprising administering to the patient an amount of a compound that inhibits the activity of the ribosomal protein identified by the methods.

USE - The method is useful for identifying compounds that modulate protease activity, as well as for assaying for protease activity. The protease modulators identified by the assays are useful as therapeutic agents against viral, bacterial or fungal infections, or **cancer**. Protease **inhibitors** or agonists identified by the method are also useful in treating contaminated items, e.g. crops, wood, metal or plastic.

ADVANTAGE - The methods are high throughput assays that are sensitive, and can be performed rapidly and without the use of radioactivity. The present method allow for the use of large, more native-like protease substrates, rather than only synthetic peptides, thus creating an assay system that more closely mimics endogenous, in vivo situations.

Dwg.0/8

L33 ANSWER 5 OF 48 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-339689 [29] WPIDS
DOC. NO. NON-CPI: N2000-254982
DOC. NO. CPI: C2000-103142
TITLE: Inhibiting CD40 signaling useful for treating conditions associated with CD40 signaling, e.g. B cell **neoplasia**, comprises **inhibiting** TRAF3 degradation to **inhibit** NFkB activation in a cell.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): ANNUNZIATA, C M; COSSMAN, J
PATENT ASSIGNEE(S): (GEOU) UNIV GEORGETOWN MEDICAL CENT
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000023590	A2	20000427	(200029)*	EN	65

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP US

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000023590	A2	WO 1999-US24567	19991019

PRIORITY APPLN. INFO: US 1998-104888P 19981020
AN 2000-339689 [29] WPIDS
AB WO 200023590 A UPAB: 20000617
NOVELTY - Inhibiting CD40 signaling, comprising inhibiting Tumor necrosis factor Receptor-associated factor (TRAF)3 degradation, to inhibit

CD40-mediated NFkappaB (NFkB) activation in a cell, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method for inhibiting the expression of interleukin (IL)-6 in a cell comprising inhibiting TRAF3 degradation in the cell;

(2) a method of treating conditions associated with CD40 signaling, comprising administering an acid/**aspartate protease** inhibitor;

(3) an inhibitor of CD40 signaling comprising an acid/**aspartate protease** inhibitor;

(4) a method for the regulation of conditions mediated by NFkB in a cell, comprising regulation of TRAF3 degradation by administering a composition to the cell which increases or decreases TRAF3 degradation, where an increase in TRAF3 degradation results in an increase in NFkB activation, and a decrease in TRAF3 degradation results in a decrease in NFkB activation;

(5) a regulator of NFkB activation, where the composition is an acid/**aspartate protease** inhibitor;

(6) a diagnostic assay for the detection of NFkB activation and/or CD40 signaling in a cell comprising detecting degradation of TRAF3 in the cell where an increase in TRAF3 degradation indicates an increase in NFkB activation;

(7) a TRAF3 degrading factor;

(8) a nucleic acid fragment comprising a TRAF3 gene containing a deletion from nucleotides 39-927 of the human TRAF3 sequence, fully defined in the specification; and

(9) a DNA molecule comprising (8) in a vector.

ACTIVITY - Cytostatic; immunosuppressive; antirheumatic; antiarthritic; neuroprotective; antiallergic.

MECHANISM OF ACTION - Inhibiting CD40 signaling, by inhibiting TRAF3 degradation.

USE - The method is useful for treating conditions associated with CD40 signaling, and for regulating NFkB mediated conditions, such as cell proliferation, protection from apoptosis, transcription of cytokine genes and transplant rejection (claimed). The conditions associated with CD40 signaling which can be treated are B- cell neoplasia, autoimmune diseases, Hodgkin's lymphoma, transplant rejection and lupus (claimed). A diagnostic assay is used to detect NFkB activation and/or CD40 signaling in a cell (claimed). The method can also be used for predicting rheumatoid arthritis, multiple sclerosis, transplant rejection, Waldenstrom's macroglobulinemia (Hyper IgM), autoimmunity, and other diseases caused by CD40 or NFkB up- or down-regulation. The recombinant or fusion protein can be used as an agent for reducing, or preferably eliminating TRAF3 degradation, NFkB activation, or CD40 signaling, as well as for identifying inhibitors of TRAF3 degradation. Cells expressing TRAF3 can be used to analyze the effectiveness of molecules, drugs or agents which inhibit TRAF3 degradation, such as host proteins or chemically derived agents or other molecules which may interact with the cell to down-regulate or alter the degradation of TRAF3, its degrading factor or cofactors needed for TRAF3 degradation. Agents which reduce, or preferably eliminate TRAF3 degradation may be used in the therapy of diseases associated with the unwanted TRAF3 degradation or diseases with unwanted CD40 activation, such as cancer (e.g. lymphoma, pre-leukemia conditions), transplant rejection, autoimmunity, allergy, and arthritis.

Dwg.0/11

L33 ANSWER 6 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:662842 HCAPLUS
DOCUMENT NUMBER: 136:334563

TITLE: Protease inhibitors as anticancer drugs: role of molecular modelling and combinatorial chemistry in drug design
AUTHOR(S): Frecer, V.; Maliar, T.; Miertus, S.
CORPORATE SOURCE: International Centre for Science and High Technology, Trieste, I-34012, Italy
SOURCE: International Journal of Medicine, Biology and the Environment (2000), 28(2), 161-173
CODEN: IMBEFQ; ISSN: 1128-935X
PUBLISHER: Medecine, Biologie, Environnement
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Several bio-mol. targets related to cancer initiation and progression have been identified in the last decade, thus offering various new strategies for cancer treatment. The survey of these strategies is presented with emphasize put on chemotherapy - focussing especially on the human proteases inhibition. A brief review of natural and synthetic protease inhibitors that are currently either in clin. praxis or in laboratory development that can block tumor cell migration, invasion, proliferation, progression and metastasis is given. Strategies of modern technologies of drug research that comprise combinatorial chemical and technol. as well as rational computer-assisted structure-based drug design utilizing mol. modeling techniques are briefly introduced. Their principles, applicability and limits are surveyed. Finally, an example of computer-assisted combinatorial chemical inhibitor design of human urokinase type plasminogen activator, which combines virtual library generation and anal. with the methods of mol. modeling, is presented illustrating recent efforts to design new drug candidates for antimetastatic therapy.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 7 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999354471 EMBASE
TITLE: Regulation of angiostatin production by matrix metalloproteinase-2 in a model of concomitant resistance.
AUTHOR: O'Reilly M.S.; Wiederschain D.; Stetler-Stevenson W.G.; Folkman J.; Moses M.A.
CORPORATE SOURCE: J. Folkman, Laboratory of Surgical Research, Dept. of Surgery, Children's Hospital, Boston, MA 02115, United States
SOURCE: Journal of Biological Chemistry, (1999) 274/41 (29568-29571).
Refs: 29
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have previously reported the identification of the endogenous angiogenesis inhibitor angiostatin, a specific inhibitor of endothelial cell proliferation in vitro and angiogenesis in vivo. In our original studies, we demonstrated that a Lewis lung carcinoma (LLC-LM) primary tumor could suppress the growth of its metastases by generating angiostatin. Angiostatin, a 38-kDa internal **fragment** of

plasminogen, was purified serum and urine of mice bearing LLC-LM, and its discovery provides the first proven mechanism for concomitant resistance (O'Reilly, M. S., Holmgren, L., Shing, Y., Chen, C., Rosenthal, R. A., Moses, M. A., Lane, W. S., Cao, Y., Sage, E. H., and Folkman, J. (1994) Cell 79, 315-328). Subsequently, we have shown that systemic administration of angiostatin can regress a wide variety of malignant tumors in vivo. However, at the time of our initial discovery of angiostatin, the source of the protein was unclear. We hypothesized that the tumor or stromal cells might produce an **enzyme** that could cleave plasminogen sequestered by the primary tumor into angiostatin. Alternatively, we speculated that the tumor cells might express angiostatin. By Northern analysis, however, we have found no evidence that the tumor cells express angiostatin or other **fragments** of **plasminogen** (data not shown). We now report that gelatinase A (matrix metalloproteinase-2), produced directly by the LLC- LM cells, is responsible for the production of angiostatin, which suppresses the growth of metastases in our original model.

L33 ANSWER 8 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 3

ACCESSION NUMBER: 1999323224 EMBASE
TITLE: Synthesis and structure activity relationships of novel small molecule cathepsin D inhibitors.
AUTHOR: Dumas J.; Brittelli D.; Chen J.; Dixon B.; Hatoum-Mokdad H.; Konig G.; Sibley R.; Witowsky J.; Wong S.
CORPORATE SOURCE: J. Dumas, Department of Chemistry Research, Bayer Corporation, Pharmaceutical Division, 400 Morgan Lane, West Haven, CT 06516, United States
SOURCE: Bioorganic and Medicinal Chemistry Letters, (6 Sep 1999) 9/17 (2531-2536).
Refs: 9
ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(99)00433-3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Cathepsin D, a lysosomal **aspartyl protease**, has been implicated in the pathology of Alzheimer's disease as well as breast and ovarian **cancer**. A weakly active cathepsin D **inhibitor** was identified by high throughput screening. Subsequent optimization led to the discovery of a new class of small molecule inhibitors of this enzyme, culminating with the sulfonamide 13 (IC50 = 250 nM).

L33 ANSWER 9 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2000:56662 HCAPLUS
DOCUMENT NUMBER: 132:332721
TITLE: Generation of angiostatin-like **fragments** from **plasminogen** by prostate-specific antigen
AUTHOR(S): Heidtmann, H. H.; Nettelbeck, D. M.; Mingels, A.; Jager, R.; Welker, H. G.; Kontermann, R. E.
CORPORATE SOURCE: St Joseph Hospital, Bremerhaven, D-27568, Germany
SOURCE: British Journal of Cancer (1999), 81(8), 1269-1273
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal

LANGUAGE: English
AB Angiostatin, a potent **inhibitor** of angiogenesis, tumor growth, and **metastasis**, is a biol. active **fragment** of **plasminogen**, containing the kringle domains 1-4. It is generated from plasminogen by limited proteolysis. The authors show that prostate-specific antigen (PSA), a serine **proteinase** secreted by human prostate and human prostate cancer cells, is able to convert Lys-**plasminogen** to biol. active angiostatin-like **fragments**, containing kringles 1-4, by limited proteolysis of peptide bond Glu439-Ala440 in vitro. In an in vitro morphogenesis assay, the purified angiostatin-like fragments inhibited proliferation and tubular formation of human umbilical vein endothelial cells with the same efficacy as angiostatin. This finding might help to understand growth characteristics of prostate cancer, which usually has low microvessel d. and slow proliferation.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 10 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:400013 HCAPLUS
DOCUMENT NUMBER: 131:179459
TITLE: Inhibition of cathepsin D by tripeptides containing statine analogs
AUTHOR(S): Bessodes, Michel; Antonakis, Kostas; Herscovici, Jean; Garcia, Marcel; Rochefort, Henri; Capony, Francoise; Lelievre, Yves; Scherman, Daniel
CORPORATE SOURCE: CNRS UMR 133, ENSCP, Paris, 75005, Fr.
SOURCE: Biochemical Pharmacology (1999), 58(2), 329-333
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Various analogs of statine, a remarkable amino acid component of the protease inhibitor pepstatine, were synthesized and evaluated as tripeptide derivs. for their activity against cathepsin D and HIV-1 protease. The analogs of statine were condensed with the C-terminal side of three different N-carbobenzyloxydipeptides: N-CBZ-Val-Val ; N-CBZ-Val-Phe; and N-CBZ-Val-Trp. The resulting tripeptides therefore included three distinctive types of derivs.: (1) a blank compound lacking the hydroxyl function on the statine analog; (2) analogs with a linear alkyl side chain, a deoxy termination and of different stereochem. ; (3) analogs bearing the iso-Pr side chain of statine with different functions on the terminal side (deoxy termination; cyano terminal group; and ester group). The tripeptide derivs. of the compds. described showed good inhibitory property and interesting selectivity with cathepsin D compared to another **aspartyl protease**, the HIV **protease** . Furthermore, significant effectiveness against cancer cell proliferation at relatively high concns. (50 μM) was evidenced. These concns. appeared at least 50-fold higher than those inhibiting cathepsin D-induced proteolysis in vitro. Although a non-specific effect cannot be excluded at such high concns., this could suggest that cellular uptake of these compds. remains a limiting factor in their action, and thus improvement in their membrane permeation should be considered. On the other hand, since tripeptides are actively absorbed through the transepithelial barrier of the gastrointestinal track, these new products could be promising as orally absorbed inhibitors of extracellular cathepsin D and as such for the therapy of some invasive tumors and metastases or for inflammation treatment.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 11 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:458339 HCAPLUS
DOCUMENT NUMBER: 132:91503
TITLE: Modulation of Proliferation and Chemosensitivity by Procathepsin D and Its Peptides in Ovarian Cancer
AUTHOR(S): Bazzett, Lisa B.; Watkins, Christopher S.; Gercel-Taylor, Cicek; Taylor, Douglas D.
CORPORATE SOURCE: Departments of Obstetrics & Gynecology, University of Louisville School of Medicine, Louisville, KY, 40292, USA
SOURCE: Gynecologic Oncology (1999), 74(2), 181-187
CODEN: GYNOA3; ISSN: 0090-8258
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Since the presence of precursors (pro-forms) of the aspartyl endoprotease, cathepsin D, appears to be linked with tumor progression, their presence was examined in sera and tumor tissues of ovarian cancer patients. The role of cathepsin D pro-forms was further assessed in the dysregulated proliferation and chemoresistance observed in advanced ovarian cancer. Cathepsin D was isolated from sera of ovarian cancer patients (n = 20) and normal volunteers (n = 11), as well as from solubilized normal ovarian epithelium (n = 8) and ovarian epithelial tumor tissue (n = 12). The specific mol. forms of cathepsin D were analyzed in these samples by Western immunoblot. Multiple circulating mol. weight forms of cathepsin D were identified in ovarian cancer patients ranging from 24 to 60 kDa, while in normal controls, a major band was observed at 34 kDa in all samples and minor bands corresponding to 27 and 48 kDa were detected in approx. half of the controls. To assess its consequences on ovarian cancer, the 52-kDa protein was immunopptd. from culture medium of an exponentially growing ovarian tumor cell line and was further purified by reverse-phase high-pressure liquid chromatog. Its effect on proliferation was assayed by determining cell doubling times and their chemosensitivity was measured in a standard cytotoxicity assay using cisplatin. In addition, decapeptides corresponding to the pro-portion of cathepsin D were analyzed in parallel. Procathepsin D and one decapeptide, peptide 2, as well as IGF-II (as a known pos.) increased cell proliferation, with doubling times of 28.4, 28.8, and 30.3 h, resp., vs. untreated UL-1 cells (36.4 h). Procathepsin D treatment of UL-1 tumor cells significantly increased the cisplatin LD50 (74.9 μg/mL) over untreated (33.9 μg/mL) as well as IGF-II-treated (38.8 μg/mL) cells. Peptide 2 also showed a significant increase in LD50 (69.5 μg/mL) compared to untreated and peptide 1-treated cells (37.1 μg/mL). There are several unique forms of cathepsin D expressed and accumulated by ovarian tumors and these forms are detectable in the sera of those with ovarian cancer. The presence of these procathepsin D can increase the proliferation of these tumor cells, while decreasing their sensitivity to chemotherapeutic agents. While procathepsin D and IGF-II both enhance proliferation, only procathepsin D (and peptide 2) appears to modulate chemosensitivity, suggesting a sep. receptor or pathway for this consequence. (c) 1999 Academic Press.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 12 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:369695 HCAPLUS
DOCUMENT NUMBER: 131:179552
TITLE: Angiostatin inhibits endothelial and melanoma cellular

invasion by blocking matrix-enhanced plasminogen activation
AUTHOR(S): Stack, M. Sharon; Gately, Stephen; Bafett, Lisa M.; Enghild, Jan J.; Soff, Gerald A.
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Northwestern University Medical School, Chicago, IL, 60611, USA
SOURCE: Biochemical Journal (1999), 340(1), 77-84
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiostatin, a **kringle**-containing **fragment** of **plasminogen**, is a potent inhibitor of angiogenesis. The mechanism(s) responsible for the anti-angiogenic properties of angiostatin are unknown. We now report that human angiostatin blocks plasmin(ogen)-enhanced in vitro invasion of tissue plasminogen activator (t-PA)-producing endothelial and melanoma cells. Kinetic analyses demonstrated that angiostatin functions as a non-competitive inhibitor of extracellular-matrix (ECM)-enhanced, t-PA-catalyzed plasminogen activation, with a Ki of 0.9±0.03 μM. This mechanism suggests that t-PA has a binding site for the inhibitor angiostatin, as well as for its substrate plasminogen that, when occupied, prevents ternary complex formation between t-PA, plasminogen and matrix protein. Direct binding expts. confirmed that angiostatin bound to t-PA with an apparent **Kd** [**Kd**(app)] of 6.7±0.7 nM, but did not bind with high affinity to ECM proteins. Together, these data suggest that angiostatin in the cellular micro-environment can inhibit matrix-enhanced plasminogen activation, resulting in reduced invasive activity, and suggest a biochem. mechanism whereby angiostatin-mediated regulation of plasmin formation could influence cellular migration and invasion.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 13 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:582912 HCAPLUS
DOCUMENT NUMBER: 129:211700
TITLE: Method for inhibition of breast tumor growth by inhibition of procathepsin D activation peptide
INVENTOR(S): Fusek, Martin; Vetvicka, Vaclav
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA
SOURCE: U.S., 18 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5800814	A	19980901	US 1994-232997	19940422
PRIORITY APPLN. INFO.:			US 1994-232997	19940422

AB Human procathepsin D was demonstrated to be mitogenic for breast cancer cells but not normal cells. The activation peptide of the procathepsin D appears to be responsible, since inhibition of enhancement of proliferation of breast cancer cells can be obtained by inhibition of the activation peptide through the use of an agent such as an antibody immunoreactive with the activation peptide.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 14 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:268324 HCAPLUS
DOCUMENT NUMBER: 128:326484
TITLE: Unique **peptides** for targeting **fibronectin**-enriched surfaces and a method for their delivery in the treatment of metastatic cancer
INVENTOR(S): Groves, Michael J.; Gao, Xiaoyan
PATENT ASSIGNEE(S): Board of Trustees of the University of Illinois, USA; Groves, Michael J.; Gao, Xiaoyan
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9817242	A1	19980430	WO 1997-US18853	19971023

W: CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1996-29509P P 19961024
AB A method for the identification of unique **fibronectin**-targeting **peptides** derived from the tryptic digestion of purified gelatin is described. Two unique peptides are isolated and shown to have higher affinities for fibronectin than the gelatin alone. The peptides are stabilized and delivered by covalently bonding to the phosphatidylethanolamine existing naturally in phospholipid-stabilized triglyceride emulsions currently employed clin. as injectable nutritional emulsions. Unexpectedly, we discovered that the peptides could be coupled to emulsion droplets in situ. One of the systems identified as the 12-mer Peptide I linked to the phosphatidylethanolamine through its N-terminus (PIN-E), is shown to retain the fibronectin-affinity of the starting material and to inhibit the spreading activity of baby hamster kidney cells, a well-recognized in vitro model of metastatic tumor spreading activity. This particular system is stable at refrigerator temperature for at least a month but demonstrates some decoupling of the peptide and aggregation of the emulsion droplets in the presence of rabbit serum at 37 °C after two days storage. It is anticipated that these systems will have utility by passively blocking metastatic processes that involve fibronectin. In addition, they would have advantages as drug delivery systems specifically targeting fibronectin-enriched surfaces, especially for hydrophobic drugs such as paclitaxel (Taxol).
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 15 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1998:390002 HCAPLUS
DOCUMENT NUMBER: 129:130938
TITLE: Upregulation of CASP genes in human tumor cells undergoing etoposide-induced apoptosis
AUTHOR(S): Droin, N.; Dubrez, L.; Eymin, B.; Renvoize, C.; Breard, J.; Dimanche-Boitrel, M. T.; Solary, E.
CORPORATE SOURCE: CJF INSERM 94-08, Biol. Therapy Cancer Group, UFR Med., Chatenay-Malabry, 21000, Fr.
SOURCE: Oncogene (1998), 16(22), 2885-2894
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton Press

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Caspases are **aspartate**-specific cysteine **proteases** that play a pivotal role in drug-induced cell death. We designed RT-PCR assays to analyze the expression of CASP-3, CASP-4, CASP-6 and the long and short isoforms of CASP-2 genes in human cells. These genes heterogeneously coexpress in leukemic cell lines and bone marrow samples from patients with de novo acute myelogenous leukemia at diagnosis. Treatment of U937 and HL60 leukemic cells and HT29 colon **carcinoma** cells with the topoisomerase II **inhibitor** etoposide upregulates CASP-2 and CASP-3 genes in these cells before inducing their apoptosis. This effect of etoposide is not observed in K562 cells and bcl-2-transfected U937 cells which are less sensitive to drug-induced apoptosis. Nuclear run-on expts. demonstrate that etoposide increases CASP gene transcription in U937 cells, an effect that is prevented by Bcl-2 overexpression. Upregulation of CASP genes is associated with an enhanced synthesis of related procaspases that precedes the appearance of apoptosis markers including caspase-3 activation, poly(ADP-ribose) polymerase cleavage and internucleosomal DNA fragmentation. These results suggest that the ability of tumor cells to upregulate CASP-2 and CASP-3 genes in response to cytotoxic drugs could be predictive of their sensitivity to drug-induced apoptosis.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 16 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1998160751 EMBASE
TITLE: Potential role for cathepsin D in p53-dependent tumor suppression and chemosensitivity.
AUTHOR: Wu G.S.; Saftig P.; Peters C.; El-Deiry W.S.
CORPORATE SOURCE: W.S. El-Deiry, Department of Medicine, Genetics and Cancer Center, University Pennsylvania School Med., Philadelphia, PA 19104, United States
SOURCE: Oncogene, (30 Apr 1998) 16/17 (2177-2183).
Refs: 31
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cathepsin D (CD), the major intracellular **aspartyl protease**, is a mediator of IFN-γ and TNF-α induced apoptosis. Using subtractive hybridization screening we isolated CD as an upregulated transcript in PA1 human ovarian cancer cells undergoing adriamycin-induced apoptosis. CD mRNA levels increased in wild-type p53-expressing PA1, ML1 leukemia and U1752 lung cancer cells but not in mutant p53-expressing cells following adriamycin exposure. Overexpression of CD inhibited growth of colon, liver, and ovarian cancer cells. CD protein expression was increased by exposure of ML1 cells to etoposide, adriamycin or γ-radiation. Inhibition of CD protease with Pepstatin A suppressed p53-dependent apoptosis in lymphoid cells, suggesting a possible role for CD in p53-dependent cell death. CD(-/-) fibroblasts were found to be more resistant to killing by adriamycin and etoposide, as compared to CD(+/+) cells. Two p53 DNA-binding sites located in the CD-promoter specifically bound to p53 protein in vitro and appeared to

mediate transactivation of a CD-promoter luciferase-reporter during p53-dependent apoptosis. These observations link CD protease to p53-dependent tumor suppression and chemosensitivity.

L33 ANSWER 17 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:464096 HCAPLUS
DOCUMENT NUMBER: 129:183956
TITLE: The characterization of cell death induced by 1-(3-C-ethynyl-β-D-ribo-pentofuranosyl)cytosine (ECyd) in FM3A cells
AUTHOR(S): Takatori, Satoshi; Tsutsumi, Shinji; Hidaka, Muneaki; Kanda, Hiroshi; Matsuda, Akira; Fukushima, Masakazu; Wataya, Yusuke
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Okayama University, Okayama, 700, Japan
SOURCE: Nucleosides & Nucleotides (1998), 17(8), 1309-1317
CODEN: NUNUD5; ISSN: 0732-8311
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The characterization of cell death induced by 1-(3-C-ethynyl-β-D-ribo-pentofuranosyl)cytosine (ECyd), a potent inhibitor of RNA synthesis, was performed using mouse mammary tumor FM3A cells in vitro. Accompanied with the cell death induced by ECyd (3.0 μM)-treatment, about 100-200 kbp-sized and internucleosomal DNA fragmentation were observed by orthogonal-field-alternation gel electrophoresis (OFAGE) and conventional gel electrophoresis, resp. **Protease** inhibitors, carbobenzoxy-L-**aspart**-1-yl[(2,6-dichlorobenzoyl)oxy]methane (Z-Asp-CH2-DCB), Nα-p-tosyl-L-lysine chloromethyl ketone (TLCK) and N-p-tosyl-L-phenylalanine chloromethyl ketone (TPCK), effectively blocked the cell death, suggesting that the proteases inhibited by Z-Asp-CH2-DCB, TLCK or PTCK were involved in the process of the cell death.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 18 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 1997:625099 HCAPLUS
DOCUMENT NUMBER: 127:302974
TITLE: Baculovirus p35 and Z-VAD-fmk **inhibit** thapsigargin-induced apoptosis of breast **cancer** cells
AUTHOR(S): Qi, Xiao-Mei; He, Huiling; Zhong, Hongying; Distelhorst, Clark W.
CORPORATE SOURCE: Department of Medicine, Case Western Reserve University/Ireland Cancer Center, Cleveland, OH, 44106, USA
SOURCE: Oncogene (1997), 15(10), 1207-1212
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Programmed cell death, or apoptosis, is inhibited by the antiapoptotic oncogene, Bcl-2, and is mediated by a cascade of **aspartate**-specific cysteine **proteases**, or caspases, related to interleukin 1β-converting enzyme. Depending on cell type, apoptosis can be induced by treatment with thapsigargin (TG); a selective inhibitor of the endoplasmic reticulum-associated calcium-ATPase. The role of caspases in mediating TG-induced apoptosis was investigated in the Bcl-2-neg. human breast cancer cell line, MDA-MB-468. Apoptosis developed in MDA-MB-468

cells over a period of 24-72 h following treatment with 100 nM TG, and was prevented by Bcl-2 overexpression. TG-induced apoptosis was associated with activation of caspase-3 and was inhibited by stable expression of the baculovirus p35 protein, an inhibitor of caspase activity. Also, TG-induced apoptosis was inhibited by treating cells with Z-VAD-fmk, a cell-permeable fluoromethylketone inhibitor of caspases. These findings indicate that TG-induced apoptosis of MDA-MB-468 breast **cancer** cells is subject to **inhibition** by Bcl-2 and is mediated by caspase activity. This model system should be useful for further investigation directed toward understanding the role of calcium in signaling apoptosis, and its relation to Bcl-2 and the caspase proteolytic cascade.

L33 ANSWER 19 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:603788 HCAPLUS
DOCUMENT NUMBER: 125:241529
TITLE: Purification and initial characterization of cathepsin D from normal human breast tissue (**aspartyl protease, protease inhibitors**, tumor **metastasis**)
AUTHOR(S): Wright, Lorinda Marie
CORPORATE SOURCE: Lehigh Univ., Bethlehem, PA, USA
SOURCE: (1996) 110 pp. Avail.: From degree-granting institution
From: Diss. Abstr. Int., B 1996, 57(5), 3191
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L33 ANSWER 20 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:528797 HCAPLUS
DOCUMENT NUMBER: 125:237573
TITLE: Biological activity of water-soluble fullerenes. Structural dependence of DNA cleavage, cytotoxicity, and enzyme inhibitory activities including HIV-protease inhibition
AUTHOR(S): Nakamura, Eiichi; Tokuyama, Hidetoshi; Yamago, Shigeru; Shiraki, Takashi; Sugiura, Yukio
CORPORATE SOURCE: School Science, University Tokyo, Tokyo, 113, Japan
SOURCE: Bulletin of the Chemical Society of Japan (1996), 69(8), 2143-2151
CODEN: BCSJA8; ISSN: 0009-2673
PUBLISHER: Nippon Kagakkai
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two different classes of water-soluble fullerene derivs., detergent-type, were synthesized. The derivs. were evaluated for their biol. activities including cytotoxicity, DNA cleavage, and inhibition of HIV-protease and other enzymes. Both classes of compds. display generally similar behavior except for their cytotoxicity spectra against several cell lines. The fullerene derivs. bearing N-methylpyrrole were found to be photo-inactive with respect to DNA cleaving activity and cytotoxicity. A study on the kinetics for the inhibition of HIV-protease with detergent type derivative revealed that the compound is a potent fullerene-based HIV protease inhibitor, inhibiting the enzyme activity in a reversible and competitive manner with a Ki value of 0.32 μM.

L33 ANSWER 21 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:522028 HCAPLUS

DOCUMENT NUMBER: 125:211985
TITLE: Promotion of heat-induced apoptosis in FM3A cells by protease inhibitors
AUTHOR(S): Zhu, Wei-Guo; Aramaki, Ryoji; Cai, Yong; Antoku, Shigetoshi
CORPORATE SOURCE: Dep. Exp. Radiol., Kyushu Univ., Fukuoka, 812-82, Japan
SOURCE: Biochemical and Biophysical Research Communications (1996), 225(3), 924-931
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Although it has been shown that proteases may play a pos. role in causing apoptosis of some cells, we report here that, on the contrary, protease inhibitors can promote heat-induced apoptosis in FM3A cells. Cysteine protease inhibitor, trans-Epoxy-succinyl-L-leucylamido-(4-guanidino)butane (E-64, 100 μg/mL) and **aspartate protease** inhibitor, pepstatin-A (100 μg/mL) were used to test hyperthermic effect on FM3A cells and showed remarkable cytotoxicity when they were present in cell suspension during heating at 44°. The cytotoxicity was due to promotion of heat-induced apoptosis as judged by DNA agarose electrophoresis. Furthermore, using flow cytometric anal., we observed a decrease in the G0/G1 phase cell and an increase in the S phase cell as well as increased apoptosis after heat shock. E-64 and pepstatin-A exhibited a promotive effect on the changes of cell cycle induced by heat. The data presented suggest that the enhancement of hyperthermic cell killing by protease inhibitors may be related to promotion of heat-induced apoptosis and changes of cell cycle.

L33 ANSWER 22 OF 48 MEDLINE on STN
ACCESSION NUMBER: 97160098 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9007614
TITLE: Cytokines may influence tumor growth and spread. An in vitro study in two human cancer cell lines.
AUTHOR: Panozzo M P; Basso D; De Paoli M; Carraro P; Burighel D; Plebani M
CORPORATE SOURCE: Department of Laboratory Medicine, University of Padua, Italy.
SOURCE: International journal of clinical & laboratory research, (1996) 26 (4) 240-4.
Journal code: 9206491. ISSN: 0940-5437.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 20000303
Entered Medline: 19970618

AB Tumor spread may be favored by a reduced production and/or an enhanced degradation of extracellular matrix components (collagen, fibronectin, laminin). Most tumor cell behavior, from growth to spread, may be regulated by cytokines, the exact roles of which, however, are not yet fully understood. We here evaluate the effects of some cytokines (epidermal growth factor, transforming growth factor-beta 1, interleukin-1 alpha, and interleukin-1 beta) on both cell growth and the production of the aminoterminal peptide of type III procollagen, the urokinase plasminogen activator, and the plasminogen activator **inhibitor**-1

in **neoplastic** cell lines originating in the pancreas and colon. Cells were stimulated daily with the above cytokines and the aminoterminal **peptide** of type III procollagen, urokinase **plasminogen** activator, and plasminogen activator inhibitor-1 were measured in the conditioned media. Epidermal growth factor stimulated cell growth of both cell lines. Transforming growth factor-beta 1 counteracted cell proliferation and stimulated type III procollagen and plasminogen activator inhibitor-1 production only in the colon cancer cell line. Interleukin-1 alpha slightly stimulated cell growth, but inhibited plasminogen activator inhibitor-1 production in both cell lines; interleukin-1 beta did not affect cell growth, but stimulated plasminogen activator inhibitor-1 production by the colon cancer cell line. Our findings suggest that transforming growth factor-beta 1 and interleukin-1 beta may have an antidiffusive effect. These results confirm that cytokine-producing cells have a potential role in stimulating or counteracting tumor growth and spread and also confirm the pivotal role of host-tumor interactions in determining the outcome of a particular neoplasia.

L33 ANSWER 23 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:415596 HCAPLUS
DOCUMENT NUMBER: 127:60079
TITLE: Clinical significance of the serine protease uPA (urokinase) and its inhibitor PAI-1 as well as the cysteine proteases cathepsin B and L in breast cancer
AUTHOR(S): Schmitt, Manfred; Thomssen, Christoph; Jaenicke, Fritz; Hoefler, Heinz; Ulm, Kurt; Magdolen, Viktor; Reuning, Ute; Wilhelm, Olaf; Graeff, Henner
CORPORATE SOURCE: Institut fur Allgemeine Pathologie und Pathologische Anatomie, Technische Universitat Munchen, Germany
SOURCE: Breast Cancer Advances in Biology and Therapeutics, Meeting of the International Association for Breast Cancer Research, 21st, Paris, July 3-5, 1996 (1996), 191-200. Editor(s): Calvo, Fabien; Crepin, Michel; Magdelenat, Henri. Libbey Eurotext: Montrouge, Fr. CODEN: 64NDA8
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with 45 refs. Proteases and their inhibitors have been implicated in tumor spread and metastasis. In breast cancer, several independent investigations have demonstrated that the serine protease uPA (urokinase-type plasminogen activator), and its inhibitor PAI-1 (plasminogen activator inhibitor type-1) and receptor (uPA-R), the **aspartyl protease** cathepsin D, as well as the cysteine proteases cathepsin B and L, are strong prognostic factors to predict disease recurrence and death. Based on the strong correlation between elevated proteolytic factors and cancer spread new tumor biol.-oriented concepts involving proteolytic factors as targets for therapy were explored, especially factors of the plasminogen activation system (uPA, PAI-1, uPA-R). Suppression of uPA or uPA-R expression by antisense oligodeoxy-nucleotides or interruption of the uPA/uPA-R interaction by antibodies directed to uPA or uPA-R, naturally occurring and synthetic uPA inhibitors, as well as recombinant and synthetic uPA and uPA-R analogs were successfully tested. In addition to the plasminogen activation system, inactivation of different proteolysis systems, e.g. matrix metalloproteases and cysteine proteases, also in addition to conventional therapy protocols, may help to reduce tumor invasion and metastasis in humans even further.

L33 ANSWER 24 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:113964 HCAPLUS
DOCUMENT NUMBER: 124:211783
TITLE: Polymeric prodrugs of mitomycin C
AUTHOR(S): Soyez, Heidi; Schacht, Etienne; De Marre, Anne; Seymour, Leonard W.
CORPORATE SOURCE: Department Organic Chemistry, University Gent, Ghent, 9000, Belg.
SOURCE: Macromolecular Symposia (1996), 103(Polymers and Medicine), 163-76
CODEN: MSYMEC; ISSN: 1022-1360
PUBLISHER: Huethig & Wepf
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Poly[N-(2-hydroxyethyl)-L-glutamine] (PHEG) prodrugs of the cytotoxic agent mitomycin C (MMC) were synthesized using peptidyl spacers to link the drug to the polymeric carrier. The influence on the length and detailed structure of the oligopeptide on the rate of drug release was investigated in buffer, in the presence of lysosomal enzymes (tritosomes, cathepsin B and D) and metalloprotease type IV collagenase. It was observed that tetra- and hexapeptide based conjugates generally release MMC more effectively than tripeptide derivs. The gly-phe-ala-leu conjugate released MMC very rapidly both in presence of lysosomal enzymes and collagenase IV. Only in the presence of the **aspartic protease** cathepsin D, the gly-phe-leu-gly-phe-leu derivative turned out to be a better substrate. In vivo studies against C26 solid tumor bearing mice suggest that PHEG-spacer-MMC conjugates act as prodrugs of MMC. Antitumor efficacy of the macromol. prodrugs was better than free MMC both in inhibition of tumor growth and increasing survival.

L33 ANSWER 25 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1995:747115 HCAPLUS
DOCUMENT NUMBER: 123:188901
TITLE: Processing of precursors to neurotensin and other bioactive peptides by cathepsin E
AUTHOR(S): Kageyama, Takashi; Ichinose, Masa; Yonezawa, Satoshi
CORPORATE SOURCE: Primate Res. Inst., Kyoto Univ., Aichi, 484, Japan
SOURCE: Journal of Biological Chemistry (1995), 270(32), 19135-40
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cathepsin E (EC 3.4.23.34), an intracellular **aspartic proteinase**, was purified from monkey intestine by simple procedures that included affinity chromatog. and fast protein liquid chromatog. Cathepsin E was very active at weakly acidic pH in the processing of chemical synthesized precursors such as the precursor to neurotensin/neuromedin, proopiomelanocortin, the precursor to xenopsin, and angiotensinogen. The processing sites were adjacent to a dibasic motif in the former 2 precursors and at hydrophobic recognition sites in the latter two. The common structural features that specified the processing sites were found in the C-terminal sequences of the active peptide moieties of these precursors; namely, the sequence Pro-Xaa-X'aa-hydrophobic amino acid was found at positions P4 through P1. Pro at the P4 position is thought to be important for directing the processing sites of the various precursor mols. to the active site of cathepsin E. Although the positions of Xaa and X'aa were occupied by various amino acids, including hydrophobic and

aromatic amino acids, some of these had a neg. effect, as typically observed when Glu/Arg and Pro were present at the P3 and P2 positions, resp. Cathepsin D was much less active or was almost inactive in the processing of the precursors to neurotensin and **related** peptides as a result of the inability of the Pro-directed conformation of the precursor mols. to gain access to the active site of cathepsin D. Thus, the consensus sequence of precursors, Pro-Xaa-X'aa-hydrophobic amino acid, might not only generate the best conformation for cleavage by cathepsin E but might be responsible for the difference in specificities between cathepsins E and D.

L33 ANSWER 26 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:625463 HCAPLUS
DOCUMENT NUMBER: 123:80589
TITLE: Selectivity of the plasminogen activator inhibitor (PAI-1) for the iso **enzyme** of guanidinobenzoatase on the surface of colonic carcinoma cells
AUTHOR(S): Steven, F. S.; Anees, M.; Booth, N. A.
CORPORATE SOURCE: School Biological Sciences, University Manchester, Manchester, M13 9PT, UK
SOURCE: Anticancer Research (1995), 15(1), 205-10
CODEN: ANTRD4; ISSN: 0250-7005
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The interaction of plasminogen activator-inhibitor (PAI-1) with a cell surface **protease**, guanidinobenzoatase (GB), has been studied in free solution and on the surface of colonic epithelial cells. It has been demonstrated that PAI-1 recognizes and inhibits the iso **enzymic** form of GB associated with colonic carcinoma cells but fails to bind to the iso **enzymic** form of GB associated with normal donor colonic epithelial cells. This interaction is mediated by a lysyl binding site on the GB: complex formation prevents GB binding to fibrin fibrils which also involves lysyl binding sites.

L33 ANSWER 27 OF 48 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 96137454 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8556577
TITLE: Urokinase-type plasminogen activator (uPA) and its receptor (CD87): a new target in tumor invasion and metastasis.
AUTHOR: Schmitt M; Wilhelm O; Janicke F; Magdolen V; Reuning U; Ohi H; Moniwa N; Kobayashi H; Weidle U; Graeff H
CORPORATE SOURCE: Frauenklinik, Technischen Universitat, Munchen, Germany.
SOURCE: Journal of obstetrics and gynaecology (Tokyo, Japan), (1995 Apr) 21 (2) 151-65. Ref: 60
Journal code: 9515066. ISSN: 1340-9654.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960312
Last Updated on STN: 20000303
Entered Medline: 19960223
AB Extravasation and intravasation of tumor cells in solid malignant tumors is controlled by 3 steps: 1) attachment to and interaction of tumor cells with components of the basement membrane and the extracellular matrix, 2)

local proteolysis, and 3) tumor cell migration. Evidence has accumulated that different types of tumor-associated proteases, their inhibitors and receptors are involved in tumor invasion and metastasis. Four different classes of proteases are known to be correlated with the malignant phenotype: 1) Matrix metalloproteases; including collagenases, gelatinases and stromelysins. 2) Cysteine proteases; including cathepsins B and L. 3) **Aspartyl protease** cathepsin D. 4) Serine proteases; including plasmin and tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). A strong independent prognostic value (relapse-free and/or overall survival) has especially been demonstrated for uPA and its **inhibitor** PAI-1 in patients with **cancer** of the breast, ovary, stomach, esophagus, colon, lung, and kidney thus predicting the course of the cancer disease. The strong correlation between elevated uPA and/or PAI-1 values in primary cancer tissues and the malignant phenotype of cancer cells has prompted to explore new tumor biology-oriented concepts in order to suppress uPA or uPA receptor (CD87) expression or to abrogate interaction of uPA with CD87. Various very different approaches to interfere with the expression or reactivity of uPA or CD87 at the gene or protein level were successfully tested including antisense oligonucleotides, antibodies, inhibitors and recombinant or synthetic uPA and CD87 analogues.

L33 ANSWER 28 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:513639 HCAPLUS
DOCUMENT NUMBER: 122:256403
TITLE: HIV **aspartate protease** inhibitors as antitumor agents
PATENT ASSIGNEE(S): Ciba-Geigy A.-G., Switz.
SOURCE: Jpn. Kokai Tokkyo Koho, 23 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06329552	A2	19941129	JP 1994-101029	19940516
PRIORITY APPLN. INFO.:			CH 1992-1492	19930517
OTHER SOURCE(S):	MARPAT 122:256403			

AB The HIV **aspartate protease** inhibitors statine-containing dipeptides, such as tert-butoxycarbonyl-5-(S)-amino-2-(R)-benzyl-4-(S)-hydroxy-6-phenylhexanoyl-L-Val-L-Phe-morpholin-4-ylamide (I), are prepared and showed antitumor activity. I inhibited the growth of human mammary gland cancer cells in female mice. Tablets were prepared containing I 1000, corn starch 680, colloidal silicate 200, magnesium stearate 20, stearic acid 50, Na CM-starch 250g, and an appropriate amount of water.

L33 ANSWER 29 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:315939 HCAPLUS
DOCUMENT NUMBER: 122:240454
TITLE: Preparation of cell adhesion protein-like peptides as cancer **metastasis inhibitor**
INVENTOR(S): Mori, Hideto; Kojima, Masayoshi; Komazawa, Hiroyuki; Saiki, Ikuo; Azuma, Ichiro
PATENT ASSIGNEE(S): Fuji Photo Film Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent

LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06298797	A2	19941025	JP 1993-84735	19930412

PRIORITY APPLN. INFO.: JP 1993-84735 19930412
OTHER SOURCE(S): MARPAT 122:240454

AB The title peptides Z:CRR (I; Z = O, S; R = oligopeptide residue comprising 3-7 amino acid residues and containing Arg-Gly-Asp as the essential constituent unit, which is preferably represented by X-Arg-Gly-Asp-Y; wherein X = Asp, Glu; Y = Ser, Thr, Val, Ser-Pro, Ser-Pro-Ala) or pharmaceutically acceptable salts are prepared A cancer **metastasis inhibitor** contains said peptide I as the active ingredient. These peptides contain a plural number of the adhesion core peptide sequence (Arg-Gly-Asp) of a cell adhesion protein, fibronectin, are not readily excreted by **enzymic** hydrolysis or metabolism, show greater cell adhesion activity than the core sequence, and maintain various biol. activities such as cancer **metastasis inhibition** and wound healing. They interact with fibronectin receptors on malignant tumor cells and prevent tumor cells from binding to fibronectin of host cells and thereby the adhesion, colonization, and destructive invasion of host cells by cancer cells. Thus, I (Z = O, R = Asp-Arg-Gly-Asp-Ser-OH) was prepared by the solution method via deprotection and condensation of intermediate Boc-Asp(OBn)-Arg(Mts)-Gly-Asp(OBn)-Ser(Bn)-OBn (Bn = CH2Ph; Mts = mesitylenesulfonyl) (preparation given) with carbonyldiimidazole and deprotection of the resulting precursor I [Z = O, R = Asp(OBn)-Arg(Mts)-Gly-Asp(OBn)-Ser(Bn)-OBn] with a mixture of CF3CO2H, CF3SO3H, thioanisole, and m-cresol.

L33 ANSWER 30 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:298602 HCAPLUS
DOCUMENT NUMBER: 122:78086
TITLE: Proportionality of protease activities in malignant cells to their metastatic potentials
AUTHOR(S): Funahashi, Takayuki; Shimamura, Mariko; Kocha, Tomoji; Fukuda, Teruo; Aoyagi, Takaaki
CORPORATE SOURCE: Showa Coll. Pharm. Sci., Tokyo, 194, Japan
SOURCE: Biological & Pharmaceutical Bulletin (1994), 17(8), 1118-20
CODEN: BPBLEO; ISSN: 0918-6158
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has been suggested that the activities of type IV collagenase and/or ectopeptidases possessed by malignant cells are related to their metastatic potentials. In the present study, we examined the activities of three aminopeptidases, two serine proteases, as well as type IV collagenase, in three kinds of cell lines of malignant cells. The activities of aminopeptidases and serine proteases, rather than of type IV collagenase, were found to the proportionate to the metastatic potentials of those cell lines. Such activities of aminopeptidases were effectively suppressed by the addition of low mol. weight inhibitors.

L33 ANSWER 31 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:462514 HCAPLUS
DOCUMENT NUMBER: 119:62514
TITLE: Saturation of tumor cell surface receptors for

urokinase-type **plasminogen** activator by amino-terminal **fragment** and subsequent effect on reconstituted basement membranes invasion

AUTHOR(S): Kobayashi, H.; Ohi, H.; Shinohara, H.; Sugimura, M.; Fujii, T.; Terao, T.; Schmitt, M.; Goretzki, L.; Chucholowski, N.; et al.

CORPORATE SOURCE: Sch. Med., Hamamatsu Univ., Hamamatsu, 431-31, Japan

SOURCE: British Journal of Cancer (1993), 67(3), 537-44
CODEN: BJCAAI; ISSN: 0007-0920

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Single-chain urokinase-type plasminogen activator (pro-uPA) is bound to a sp. surface receptor on ovarian cancer HOC-I cells that is incompletely saturated Saturation of uncovered receptors by uPA polypeptides with intact amino-terminal fragment (ATF) derived from pro-uPA by limited proteolysis (human leukocyte elastase [HLE] or V8 **protease**) has been studied. HOC-I cells preferentially invaded reconstituted basement membranes in a time- and plasminogen-dependent manner. This process was inhibitable by preincubation with uPA polypeptides in the medium at levels which suggested that complete saturation of cell surface uPA receptors occurred. This result indicates that occupation of uPA receptors by **enzymically** inactive uPA fragments or prevention of rebinding of pro-uPA synthesized by tumor cells to the receptors specifically reduces the invasion of the tumor cells through basement membranes in vitro.

L33 ANSWER 32 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1992:401810 HCAPLUS

DOCUMENT NUMBER: 117:1810

TITLE: Glial antiproliferative proteins

INVENTOR(S): Muir, David F., IV; Manthorpe, Marston C.; Varon, Silvio S.

PATENT ASSIGNEE(S): University of California, Oakland, USA

SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9204442	A1	19920319	WO 1991-US6476	19910909
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MC, MG, MN, MW, NO, PL, RO, SD, SU				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
AU 9188646	A1	19920330	AU 1991-88646	19910909
PRIORITY APPLN. INFO.:			US 1990-579929	19900907
			WO 1991-US6476	19910909

AB Glial antiproliferative proteins comprise a neural antiproliferative protein (NAP) of .apprx.55 kD produced by glial cells and having a metalloprotease activity, and cryptic antiproliferative **fibronectin fragments** (CAFF) comprising those **fibronectin fragments** generated by action of the NAP **protease** on fibronectin and having the property of inhibiting the growth of glial cells. The NAP and CAFF glial antiproliferative proteins are useful in promoting regeneration of nervous tissue following trauma of injury or surgery, and in retarding the growth of glial tumors. Monoclonal antibodies to the glial antiproliferative proteins are useful

in the treatment of demyelinating diseases, such as multiple sclerosis.

L33 ANSWER 33 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:537663 HCAPLUS
DOCUMENT NUMBER: 117:137663
TITLE: Antitumor molecules which bind to a tumor cell and inhibit a tumor-associated **protease**
INVENTOR(S): Ballance, David James; Courtney, Michael George
PATENT ASSIGNEE(S): Delta Biotechnology Ltd., UK
SOURCE: Brit. UK Pat. Appl., 57 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2246779	A1	19920212	GB 1990-17083	19900803
GB 2246779	B2	19940817		
WO 9202553	A1	19920220	WO 1991-GB1322	19910802
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
AU 9183185	A1	19920302	AU 1991-83185	19910802
PRIORITY APPLN. INFO.:			GB 1990-17083	19900803
			WO 1991-GB1322	19910802

AB Mols. comprising a 1st region which binds to a tumor cell and a 2nd region which inhibits a tumor-associated **protease** are prepared for treating tumors. The 2 regions may be combined by chemical linking them or by expressing a nucleotide sequence encoding the 2 regions as a single polypeptide in a host transformed with the nucleotide sequence. Recombinant preparation of fusion proteins containing a methionine residue followed by amino acid residues 1-47 of urokinase-type plasminogen activator (uPA) and then plasminogen activator inhibitor 2 (PAI-2) or α1-antitrypsin Pittsburgh is described.

L33 ANSWER 34 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:210009 HCAPLUS
DOCUMENT NUMBER: 116:210009
TITLE: Purification and characterization of a cathepsin D protease from bovine chromaffin granules
AUTHOR(S): Krieger, Timothy J.; Hook, Vivian Y. H.
CORPORATE SOURCE: Dep. Biochem., Uniformed Serv. Univ. Health Sci., Bethesda, MD, 20814, USA
SOURCE: Biochemistry (1992), 31(17), 4223-31
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purification of potential tachykinin and enkephalin precursor-cleaving enzymes from bovine chromaffin granules was undertaken using as substrates the model precursors [35S](Met)-β-preprotachykinin ([35S](Met)-β-PPT) and [35S](Met)-preproenkephalin ([35S](Met)-PPE). Purification by Con A-Sepharose, Sephacryl S200, and chromatofocusing resulted in a chromaffin granule **aspartyl** protease (CGAP) that preferred the tachykinin over the enkephalin precursor. CGAP was composed of 47-, 30-, and 16.5-kDa polypeptides migrating as a single band in a nondenaturing electrophoretic gel system and coeluting with an apparent mol. mass of 45-55 kDa by size-exclusion chromatog. These results suggest that two

forms exist: a single 47-kDa polypeptide and a complex of 30±16.5-kDa-associated subunits. CGAP was optimally active at pH 5.0-5.5, indicating that it would be active within the acidic intragranular environment. Cleavage at basic residues was suggested by HPLC and high-voltage electrophoresis identification of [35S](Met)-NKA-Gly-Lys (NKA = neurokinin A) as the major acid-soluble product generated from [35S](Met)-β-PPT. Neuropeptide K was cleaved at a Lys-Arg basic residue site, as determined by identification of proteolytic products by microsequencing and amino acid composition analyses. Structural studies showed that the three CGAP polypeptides were similar to bovine cathepsin D in NH2-terminal sequences and amino acid compns., indicating that CGAP appears to be a cathepsin D-**related** protease or cathepsin D itself. The 47- and 16.5-kDa polypeptides of CGAP possessed identical NH2-terminal sequences, suggesting that the 16.5-kDa polypeptide may be derived from the 47-kDa form by proteolysis. CGAP resembled cathepsin D by cleaving at hydrophobic residues, as shown by CGAP cleavage of neuropeptide K between Leu-Tyr and Phe-Val residues. Processing of proendothelin to endothelin, present in chromaffin granules, requires processing at both hydrophobic and paired basic residues, which would be compatible with CGAP's of cleavage site specificity. In addition, CGAP's cathepsin D-like cleavage specificity for hydrophobic residues suggests that it may also be involved in degrading precursor segments that are not part of the active peptide sequences. In summary, CGAP shows substrate selectivity, and cleaves at paired basic residues and at hydrophobic residues. These properties may be compatible with possible participation of CGAP in cleaving some peptide precursors.

L33 ANSWER 35 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:469826 HCAPLUS
DOCUMENT NUMBER: 115:69826
TITLE: Human immunodeficiency virus particles free of nucleic acid and replication-incompetent, for use as antiviral agents and antigens
INVENTOR(S): Haffar, Omar K.; Hu, Shiu Lok; Senear, Allen W.; Travis, Bruce M.
PATENT ASSIGNEE(S): Oncogen, L. P., USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9107425	A1	19910530	WO 1990-US6798	19901120
W: AU, CA, FI, HU, JP, KR, NO				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2068713	AA	19910521	CA 1990-2068713	19901120
AU 9169055	A1	19910613	AU 1991-69055	19901120
AU 636944	B2	19930513		
ZA 9009302	A	19910925	ZA 1990-9302	19901120
EP 502105	A1	19920909	EP 1991-900526	19901120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
HU 60506	A2	19920928	HU 1992-1659	19901120
JP 05503629	T2	19930617	JP 1991-501082	19901120
FI 9202277	A	19920519	FI 1992-2277	19920519
NO 9201969	A	19920626	NO 1992-1969	19920519

PRIORITY APPLN. INFO.: US 1989-439205 19891120
WO 1990-US6798 19901120

AB Nucleic acid-free human immunodeficiency virus particles are prepared for use in vaccination against, prophylaxis, or treatment of human immunodeficiency virus infection. The particles are prepared by expression of genes for structural proteins in animal cell culture. Expression constructs for the expression of these genes in animal cell culture using animal virus or animal gene regulatory elements were prepared by standard methods. The use of the particles to block infection in vitro of animal cells and of peripheral blood lymphocytes from seropos. individuals is demonstrated. The use of the particles as antigens in rabbits is also demonstrated.

L33 ANSWER 36 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:32640 HCAPLUS
DOCUMENT NUMBER: 118:32640
TITLE: Effects of synthetic peptides and **protease** inhibitors on the interaction of a human ovarian cancer cell line (NIH:OVCAR-3) with a reconstituted basement membrane (matrigel)
AUTHOR(S): Kanemoto, Tomoko; Martin, George R.; Hamilton, Tom C.; Fridman, Rafael
CORPORATE SOURCE: Lab. Dev. Biol. Anomalies, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA
SOURCE: Invasion & Metastasis (1991), 11(2), 84-92
CODEN: INVMDJ; ISSN: 0251-1789
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have investigated the adhesive properties and invasiveness of cells of the human ovarian carcinoma line, NIH:OVCAR-3, in vitro. OVCAR-3 cells exhibited a similar rate of adhesion to all substrates tested including laminin, fibronectin, and collagens I and IV. The synthetic peptide YIGSR-NH2, which corresponds to an attachment site in laminin, inhibited the adhesion of the cells to laminin, but not to fibronectin. In contrast, a GRGDS-NH2 **peptide** blocked adhesion to **fibronectin** but not to laminin. OVCAR-3 cells invaded and formed branched colonies on Matrigel. Colony formation was retarded by both YIGSR-NH2 and GRGDS-NH2 peptides. Serine **protease** inhibitors and human recombinant TIMP, the tissue inhibitor of metalloproteases, inhibited ovarian tumor cell invasion while a synthetic collagenase IV inhibitor (SC-44463) had no effect. These studies suggest that metalloproteases other than collagenase IV may be important for the invasive activity of ovarian cancer cells. It is possible that synthetic peptides with antiadhesive cellular activity and certain antiproteases could be used to control the progressive colonization and invasion of peritoneal surfaces by malignant ovarian cancer cells.

L33 ANSWER 37 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:240309 HCAPLUS
DOCUMENT NUMBER: 112:240309
TITLE: Skin preparations containing protease inhibitors for reducing the risk of sunlight and ultraviolet light-induced skin cancer
INVENTOR(S): Ryan, Clarence A.
PATENT ASSIGNEE(S): Washington State University Research Foundation, Inc., USA
SOURCE: U.S., 5 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4906457	A	19900306	US 1988-241039	19880906
WO 9107166	A1	19910530	WO 1989-US5178	19891116
W: AT, AU, BB, BG, BR, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, ES, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
AU 9050257	A1	19910613	AU 1990-50257	19891116
PRIORITY APPLN. INFO.:			US 1988-241039	19880906
			WO 1989-US5178	19891116

AB The title compns. comprise ≥1 protease inhibitor at 10 pg-10 mg/mL of the composition Preferred protease inhibitors include serine protease inhibitors and metallo protease inhibitors. The composition further contains a suitable sunscreen agent to provide advantageous compns. for reducing the risk of sunlight-induced skin cancer. A com. available suntan lotion (Sea and Ski) with sun protection factor 6 was mixed with the soybean-derived Bowman Birk inhibitor at 1 mg/mL of the lotion.

L33 ANSWER 38 OF 48 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1990:428319 BIOSIS
DOCUMENT NUMBER: PREV199090089120; BA90:89120
TITLE: ANTI-METASTATIC AND ANTI-INVASIVE EFFECTS OF POLYMERIC ARG-GLY-ASP RGD PEPTIDE POLY-RGD AND ITS ANALOGUES.
AUTHOR(S): SAIKI I [Reprint author]; MURATA J; MATSUNO K; OGAWA R; NISHI N; TOKURA S; AZUMA I
CORPORATE SOURCE: INST IMMUNOLOGICAL SCI, HOKKAIDO UNIV, KITA-15, NISHI-7, KITA-KU, SAPPORO 060, JPN
SOURCE: Japanese Journal of Cancer Research, (1990) Vol. 81, No. 6-7, pp. 660-667.
CODEN: JJCREP. ISSN: 0910-5050.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 22 Sep 1990
Last Updated on STN: 22 Sep 1990

AB We have investigated the anti-metastatic and anti-invasive activities of polypeptide analogues based on the Arg-Gly-Asp (RGD) adhesive signal in fibronectin poly(RGD), poly(RGDS)[Arg-Gly-Asp-Ser] and T poly(RGDT)[Arg-Gly-Asp-Thr]. These polypetides containing repetitive RGD sequences were able to **inhibit** experimental and spontaneous lung **metastases** of B16-BL6 cells more effectively than the corresponding monomer peptides. In the spontaneous metastasis model, multiple i.v. administration of these polymeric peptides before or after surgical excision of the primary tumor resulted in a significant reduction of lung tumor colonies. However, there was no significant difference in ability to **inhibit** spontaneous lung **metastasis** among poly(RGD), poly(RGDS) and poly(RGDT), although the carboxy-terminal amino acid residue (i.e., Xaa in -RGDXaa-) has been shown to play an important role in the expression of cell adhesive character. The treatment with poly(RGD) substantially prolonged the survival time for mice injected s.c. with B16-BL6 melanoma as compared with the untreated control. We also found that the polypeptides were potently able to inhibit the invasion and migration of tumor cells in vitro. Since these polypeptide analogues

showed no antigenicity in the host and had no toxic effect on tumor cells in vitro, they may be potentially useful in the prevention of cancer metastasis.

L33 ANSWER 39 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:16254 HCAPLUS
DOCUMENT NUMBER: 112:16254
TITLE: Targeted delivery of drugs and diagnostic agents using carriers which promote endothelial and epithelial uptake and lesional localization
INVENTOR(S): Ranney, David F.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8807365	A2	19881006	WO 1988-US1096	19880330
WO 8807365	A3	19881117		
W: AT, AU, BB, BG, BR, CH, DE, DK, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU, US				
RW: AT, BE, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
US 4925678	A	19900515	US 1987-33432	19870401
AU 8816275	A1	19881102	AU 1988-16275	19880330
AU 607494	B2	19910307		
EP 352295	A1	19900131	EP 1988-903702	19880330
EP 352295	B1	19930616		
EP 352295	B2	19960410		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 04504404	T2	19920806	JP 1988-503579	19880330
JP 2886171	B2	19990426		
AT 90554	E	19930715	AT 1988-903702	19880330
CA 1324080	A1	19931109	CA 1988-565119	19880426
US 5108759	A	19920428	US 1989-448121	19891208
PRIORITY APPLN. INFO.:			US 1987-33432	19870401
			EP 1988-903702	19880330
			WO 1988-US1096	19880330

AB Targeted delivery systems comprise drugs or diagnostic agents and carriers which recognize determinants present on normal or diseased endothelium. This induces the following effects in vivo: (1) rapid endothelial envelopment of the carrier; (2) sequestration of the carrier and protection of the entrapped agent from early blood clearance; (3) acceleration of the carrier's transport across the vascular endothelium into the interstitium; and (4) improvement of drug delivery across the endothelium, so that a lower total drug dose is required. Aqueous cisplatin (I) was mixed with heparin at a 1:1.1 weight ratio and ultrasonicated to form a heparin-coated I microemulsion with particle sizes of 0.2-1.5 μm, which was stable for >1 h at 22°. Mice receiving this emulsion i.v. showed moderate to intense concentration of I in the lung interstitia, alveolar pneumocytes, respiratory epithelia, and lymph nodes, but low I concns. in the liver, whereas mice receiving standard aqueous I showed intense I concentration in the liver and almost no I in the lungs. Thus high concns. of I

(which are usually toxic to endothelium) can be successfully reformulated as a heparin microemulsion, and the heparin component can induce endothelial binding and transcellular uptake of the complexes in a fashion that protects the endothelium from the toxic effects of the drug.

L33 ANSWER 40 OF 48 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 88327732 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3416307
TITLE: Inhibition by human recombinant tissue inhibitor of metalloproteinases of human amnion invasion and lung colonization by murine B16-F10 melanoma cells.
AUTHOR: Schultz R M; Silberman S; Persky B; Bajkowski A S; Carmichael D F
CORPORATE SOURCE: Department of Biochemistry, Loyola University of Chicago, Stritch School of Medicine, Maywood, Illinois 60153.
CONTRACT NUMBER: CA43305 (NCI)
CA44659 (NCI)
SOURCE: Cancer research, (1988 Oct 1) 48 (19) 5539-45.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198810
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19980206
Entered Medline: 19881025

AB The human tissue inhibitor of metalloproteinases (TIMP) is a glycoprotein with a molecular weight of 28,000. It appears to be ubiquitous in human mesoderm tissues and has previously been shown to be identical to the collagenase inhibitor isolated from human skin fibroblasts. TIMP inhibits type I- and IV-specific collagenases and other neutral metalloendoproteinases that may be responsible for the degradation of extracellular matrix in tumor cell metastasis. In this work we have utilized recombinant human TIMP (rTIMP) obtained by expression of its cDNA gene (Carmichael et al., Proc. Natl. Acad. Sci. USA, 83:2407, 1986). The rTIMP is shown to have similar inhibition properties as natural TIMP against human skin fibroblast collagenase. In an in vitro amnion invasion assay system, rTIMP inhibited the invasion of B16-F10 murine melanoma cells through the human amniotic membrane at an identical concentration to that reported previously for natural TIMP. The mechanism by which rTIMP inhibits amniotic membrane invasion was compared to the mechanism by which the **fibronectin** receptor binding **peptide** RGDS and the aminin receptor binding peptide YIGSR inhibit amnion invasion. RGDS and YIGSR inhibited strong binding of the tumor cells to the amniotic membrane. In contrast rTIMP did not inhibit the cell adhesion step in amnion invasion, but actually increased the number of tumor cells that were tightly bound to the amnion. Thus rTIMP appears to inhibit a later step in the amnion invasion process, following B16-F10 cell adhesion. C57BL/6 mice treated with i.p. injections of rTIMP every 12 h for 6.5 days showed a significant **inhibition** of **metastatic** lung colonization by B16-F10 murine melanoma cells. While the rTIMP **inhibited** the number of **metastatic** lung tumors formed, it had no significant effect on the size of the lung tumors. Furthermore, tumors grown s.c. in mice receiving 12-h i.p. injections of rTIMP for 6.5 days, as in the in vivo colonization assay, showed no difference in size from controls. Thus the anticolonization effect of rTIMP appears not be due to an effect on tumor growth, but on the invasion step itself. The inhibition of lung colonization in C57BL/6 mice by rTIMP is one of the

first examples showing an antimetastatic effect of a selective metalloproteinase inhibitor in a mammalian animal model, and supports an essential role for metalloproteinase(s) in the extravasation and invasion of tumor cells during lung colonization by blood-borne tumor cells.

L33 ANSWER 41 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1989:37289 HCAPLUS
DOCUMENT NUMBER: 110:37289
TITLE: Inhibition of tumor cell-induced platelet aggregation and experimental tumor metastasis by the synthetic Gly-Arg-Gly-Asp-Ser peptide
AUTHOR(S): Ugen, Kenneth E.; Mahalingam, Meera; Klein, Paul A.; Kao, Kuo Jang
CORPORATE SOURCE: Coll. Med., Univ. Florida, Gainesville, FL, 32610, USA
SOURCE: Journal of the National Cancer Institute (1988), 80(18), 1461-6
CODEN: JNCIEQ; ISSN: 0027-8874
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism by which the murine fibrosarcoma clone PAK 17.15 induces platelet aggregation [tumor cell-induced platelet aggregation (TCIPA)] was studied because platelet activation by this clone is necessary for metastasis to the lungs. PAK 17.15 TCIPA was completely inhibited by ADP-clearing **enzymes**, such as apyrase, or a mixture of creatine phosphate and creatine phosphokinase. Thrombin and collagen were not involved in PAK 17.15 TCIPA. Further studies showed that ADP is most likely secreted from activated platelets and that membrane protein(s) on PAK 17.15 cells are responsible for platelet activation. Inasmuch as ADP-dependent platelet aggregation requires fibrinogen and can be inhibited by the Gly-Arg-Gly-Asp-Ser (GRGDS) synthetic peptide, the effect of this peptide on PAK 17.15 TCIPA was studied. PAK 17.15 TCIPA was completely inhibited by the GRGDS peptide (0.4 mM) but not by a control peptide, Gly-Arg-Gly-Glu-Ser (0.8 mM). In addition, the GRGDS peptide inhibited adhesion of PAK 17.15 cells to immobilized fibronectin. As expected, the GRGDS peptide almost completely inhibited lung colonization by i.v. injected PAK 17.15 cells in C57BL/6 mice. Thus, GRGDS may **inhibit** pulmonary **metastases** by interfering with TCIPA as well as with tumor cell adhesion to extracellular matrix components in the host.

L33 ANSWER 42 OF 48 MEDLINE on STN
ACCESSION NUMBER: 89088285 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3145027
TITLE: Structure, function, regulation and clinical significance of the 52K pro-cathepsin D secreted by breast **cancer** cells.
AUTHOR: Rochefort H; Augereau P; Briozzo P; Capony F; Cavailles V; Freiss G; Garcia M; Maudelonde T; Morisset M; Vignon F
CORPORATE SOURCE: Unite Hormones et Cancer, INSERM U 148, Montpellier, France.
SOURCE: Biochimie, (1988 Jul) 70 (7) 943-9.
Journal code: 1264604. ISSN: 0300-9084.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198902
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308

Entered Medline: 19890223

AB In estrogen-receptor-positive human breast **cancer** cell lines (MCF7, ZR75-1), estrogens specifically increase the secretion into the culture medium of a 52,000 Da (52K) glycoprotein and stimulate cell proliferation. The 52K protein has been purified to homogeneity using monoclonal antibodies and identified as the secreted **precursor** of a **cathepsin D** bearing mannose-6-phosphate signals. The secreted precursor 52K protein is mitogenic in vitro in estrogen-deprived MCF7 cells, can be taken up by these cells via mannose-6-phosphate receptors, and can degrade extracellular matrix and proteoglycans following its auto-activation. The protease is also produced constitutively by ER-negative cell lines, and is inducible by tamoxifen in some antiestrogen-resistant variants. The corresponding cDNA has been cloned using N-terminal sequencing of the protein and monoclonal antibodies. Its complete sequencing indicates a strong homology with pro-cathepsin D of normal tissues. Using a cDNA probe, the regulation of 52K cathepsin D mRNA by estrogens and antiestrogens has been studied and chromosome localization determined by in situ hybridization. Clinical studies using both immunohistochemistry and immunoenzymatic assay of breast **cancer** cytosol have shown that the concentration of total cellular cathepsin D (52K + 48K + 34K) is **related** to the proliferation of mammary ducts and to the prognosis of breast **cancer**. Its cytosolic concentration in primary tumors of postmenopausal patients is correlated slightly with lymph node invasion and significantly with shorter disease-free intervals in a 6-year retrospective study with the Danish Breast **Cancer** Groups and Finsen Institute (S. Thorpe et al.).(ABSTRACT TRUNCATED AT 250 WORDS)

L33 ANSWER 43 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1988:470869 HCAPLUS
DOCUMENT NUMBER: 109:70869
TITLE: Inhibitors of guanidinobenzoatase and their possible role in cell migration
AUTHOR(S): Steven, Frank S.; Griffin, Margaret M.
CORPORATE SOURCE: Sch. Biol. Sci., Univ. Manchester, Manchester, M13 9PT, UK
SOURCE: Biological Chemistry Hoppe-Seyler (1988), 369(Suppl.), 137-43
CODEN: BCHSEI; ISSN: 0177-3593
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Guanidinobenzoatase is a cell surface **protease** associated with cells capable of migration; this **enzyme** is trypsinlike and cleaves the link **peptide** Gly-Arg-Gly-Asp of **fibronectin**. A fluorescent probe, 9-aminoacridine, was used to locate cells possessing guanidinobenzoatase by fluorescent microscopy. 9-Aminoacridine is a competitive inhibitor of this **enzyme** and does not react with the cell-bound **enzyme** when the latter is already inhibited by a tissue-specific protein inhibitor of guanidinobenzoatase. Normal and tumor-bearing tissues demonstrated the presence of tissue-specific inhibitors of guanidinobenzoatase and were used to exchange inhibitors on the cell-bound guanidinobenzoatase. The activity of the **enzyme** in vivo is suppressed by the presence of inhibitors; the latter may be displaced by oxidative disulfide exchange reactions resulting in regain of **enzymic** activity on the cell surface. These inhibitors may control cell migration in vivo.

L33 ANSWER 44 OF 48 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1988:462583 BIOSIS
DOCUMENT NUMBER: PREV198886104302; BA86:104302
TITLE: STUDIES ON THE ACTIVITY OF A **PROTEASE** ASSOCIATED WITH CELLS AT THE ADVANCING EDGE OF HUMAN TUMOR MASSES IN FROZEN SECTIONS.
AUTHOR(S): STEVEN F S [Reprint author]; GRIFFIN M M; MAIER H; WEIDAUER H; MANGEL W F; ALTMANNSBERGER M
CORPORATE SOURCE: DEP BIOCHEM MOL BIOL, SCH BIOL SCI, UNIV MANCHESTER, MANCHESTER M13 9PT, UK
SOURCE: British Journal of Cancer, (1988) Vol. 58, No. 1, pp. 57-60.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 18 Oct 1988
Last Updated on STN: 18 Oct 1988

AB A fluorescent probe has been employed to study the status of a tumour associated **protease**, guanidinobenzoatase, in frozen sections of human tumours obtained from the head and neck regions. The results indicate that in vivo a naturally occurring inhibitor of gunidinobenzoatase effectively controls the activity of this **enzyme** on the majority of cells in a tumor mass. This inhibitor can be artifically displaced by formaldehyde treatment of the frozen sections and this treatment reveals the extent of latent **enzyme** in the section. In the frozen sections it was noticed that at the advancing edges of the tumour mass, the tumour cells possessed uninhibited guanidinobenzoatase, an **enzyme** known to degrade the link **peptide** between cells and **fibronectin**. It was shown that a synthetic inhibitor of guanidinobenzoatase selectively inhibited the guanidinobenzoatase of the tumour cells at the advancing edge of the tumour mass. It is suggested that the guanidinobenzoatase on cells at the leading edge of the tumour mass plays an important role in the invasion of adjacent host tissue. This synthetic inhibitor of guanidinobenzoatase has no inhibitory action on other trypsin-like **enzymes** and might therefore be of value in limiting the growth of the tumour mass in vivo.

L33 ANSWER 45 OF 48 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 88006873 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3654255
TITLE: The estrogen-regulated 52K-cathepsin-D in breast **cancer**: from biology to clinical applications.
AUTHOR: Rochefort H; Capony F; Augereau P; Cavailles V; Garcia M; Morisset M; Freiss G; Maudelonde T; Vignon F
CORPORATE SOURCE: Unite d'Endocrinologie Cellulaire et Moleculaire de l'INSERM (U 158), Montpellier, France.
SOURCE: International journal of radiation applications and instrumentation. Part B, Nuclear medicine and biology, (1987) 14 (4) 377-84.
Journal code: 8611098. ISSN: 0883-2897.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198711
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 20000303
Entered Medline: 19871119

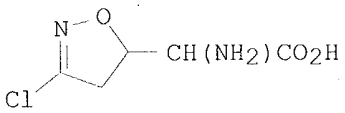
AB We have studied estrogen-regulated proteins in an attempt to understand

the mechanism by which estrogens stimulate cell proliferation and mammary **carcinogenesis**. In estrogen receptor positive human breast **cancer** cell lines (MCF7, ZR75-1) estrogens specifically increase the production into the culture medium of a 52,000 daltons (52K) glycoprotein. Several high affinity monoclonal antibodies to the partially purified secretory 52K protein have allowed to purify to homogeneity this protein and its cellular processed products. The 52K protein has been identified as the secreted **precursor** of a **cathepsin-D** like protease bearing mannose-6-phosphate signals and routed to lysosomes via mannose-6-phosphate receptor. The protease is mitogenic in vitro on estrogen deprived MCF7 cells and is able to degrade basement membrane and proteoglycans following its activation. The cellular **related** proteins, as detected by immunohistochemistry and immunoassay are more concentrated in proliferative mammary ducts than in resting ducts and their concentration in breast **cancer** cytosol appears to be more correlated with lymph nodes invasion and disease free survival (with S. Thorpe, Copenhagen) than with the estrogen receptor (RE) level. The protein is also produced constitutively by RE-negative cell lines, while in some antiestrogen resistant variants, it becomes inducible by tamoxifen, contrary to the wild type MCF7 cells. Cloning of its cDNA in lambda gt11 has allowed to show that the mRNA is rapidly induced by estrogens and to sequence the protein and compare it to that of the normal human kidney cathepsin-D.(ABSTRACT TRUNCATED AT 250 WORDS)

L33 ANSWER 46 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1985:536377 HCAPLUS
DOCUMENT NUMBER: 103:136377
TITLE: Cloning and sequence analysis of cDNA for human cathepsin D
AUTHOR(S): Faust, Phyllis L.; Kornfeld, Stuart; Chirgwin, John M.
CORPORATE SOURCE: Sch. Med., Washington Univ., St. Louis, MO, 63110, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1985), 82(15), 4910-14
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An 1110-base-pair cDNA clone for human cathepsin D was obtained by screening a λgt10 human hepatoma G2 cDNA library with a human renin exon 3 genomic fragment. Poly(A)+ RNA blot anal. with this cathepsin D clone demonstrated a message length of .apprx.2.2 kilobases. The partial clone was used to screen a size-selected human kidney cDNA library, from which 2 cathepsin D recombinant plasmids with inserts of ≈2200 and 2150 base pairs were obtained. The nucleotide sequences of these clones and of the λgt10 clone were determined The amino acid sequence predicted from the cDNA sequence shows that human cathepsin D consists of 412 amino acids with 20 and 44 amino acids in a pre- and a prosegment, resp. The mature protein region shows 87% amino acid identity with porcine cathepsin D but differs in having 9 addnl. amino acids. Two of these are at the terminus; the other 7 are positioned between the previously determined junction for the light and heavy chains of porcine cathepsin D. A high degree of sequence homol. was observed between human cathepsin D and other aspartyl proteases, suggesting a conservation of 3-dimensional structure in this family of proteins.

L33 ANSWER 47 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1980:525428 HCAPLUS
DOCUMENT NUMBER: 93:125428
TITLE: **Protease**-activated "prodrugs" for cancer

chemotherapy
AUTHOR(S): Carl, Philip L.; Chakravarty, Prasun K.; Katzenellenbogen, John A.; Weber, Michael J.
CORPORATE SOURCE: Dep. Chem., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1980), 77(4), 2224-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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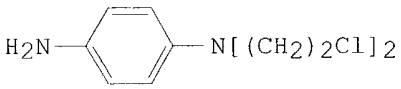

II

AB Coupling of peptide specifiers to anticancer drugs creates prodrugs which are locally activated by tumor-associated plasmin [9001-90-5] and consequently are less toxic to normal cells. Peptidyl prodrugs of the structure D-Val-Leu-Lys-X were synthesized in which the peptidyl portion was designed to allow the prodrug to serve as an excellent plasmin substrate and X was an anticancer drug either the glutamine analog (αS, 5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT-125) (I) or the alkylating agent N,N-bis(2-chloroethyl)-p-phenylenediamine (phenylenediamine mustard) (II). Treatment of these prodrugs with plasmin generated the free peptide and the free drug, demonstrating that these prodrugs are plasmin substrates. The prodrugs and free drugs were tested in vitro against either normal chicken embryo fibroblasts, which display a low level of plasminogen [9001-91-6] activator, or their virally transformed counterparts, which produce high levels of plasminogen activator. In each case the peptidyl prodrugs displayed ≥5-fold increase in selectivity for the transformed cells compared to the free drug.

L33 ANSWER 48 OF 48 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1974:22802 HCAPLUS
DOCUMENT NUMBER: 80:22802
TITLE: Effect of sarcolysine on metabolism in the organism of intact and tumorous rats
AUTHOR(S): Katkuviene, J.; Abartiene, D.; Liutkiene, R.; Malachovskis, A.
CORPORATE SOURCE: Inst. Biochem., Vilnius, USSR
SOURCE: Lietuvos TSR Mokslu Akademijos Darbai, Serija C: Biologijos Mokslai (1973), (2), 191-7
CODEN: LMDCAO; ISSN: 0131-3851
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Sarcolysine [531-76-0] (2 mg/kg, i.p.) administered to healthy rats daily for 10-15 days decreased the nonesterified fatty acid, cholesterol, total glutathione, residual N, and urea levels, and the alanine aminotransferase, lipase, and protease content of the blood. The β/α lipoprotein ratio and the blood lecithin content were elevated in normal rats. When administered to rats with transplanted sarcoma M-1 tumors, sarcolysine increased the total lecithin β/α lipoprotein ratio, free and total glutathione levels, residual N, and aspartate aminotransferase activity, while decreasing the

lipase and alanine aminotransferase activities and the urea and nonesterified fatty acid levels. Sarcolysine treatment apparently normalized only the total glutathione level and **protease** and **aspartate** aminotransferase activities in tumor-bearing rats.